

U.S. Patent Application Serial No. 10/779,399
Supplemental Amendment and Response dated November 21, 2006
Supplemental to Response to Restriction Requirement filed November 2, 2006

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Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) A crystal of BTK kinase domain of SEQ ID NO:4 having a space group of $P2_12_12_1$ and a unit cell having the dimensions of a , b , and c , where a is 45 Å plus or minus 5 Å, b is 104 Å plus or minus 10 Å, and c is 116 Å plus or minus 10 Å.

2. (Previously Presented) The crystal of claim 1, having the structural coordinates listed in Table 1.

3-15. (Canceled)

16. (Currently Amended) A method for identifying a compound that modulates BTK activity comprising:

obtaining the crystal of claim 1;

determining structural coordinates of said crystal, wherein said structural coordinates comprise the coordinates listed in Table 1;

using said ~~structure~~ structural coordinates of the crystal of claim 2 and listed in Table 1 to construct a model of said crystal including the BTK kinase domain binding pocket; and
designing a compound that complements the crystal's BTK kinase domain binding pocket.

17. (Currently Amended) A method for identifying a compound that modulates BTK activity comprising:

obtaining the crystal of claim 1;

determining atomic coordinates of said crystal, wherein said atomic coordinates comprise the coordinates listed in Table 1;

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~~providing the atomic coordinates of the crystal of claim 2; and~~
using the atomic coordinates of the crystal and a molecular modeling technique to identify a compound that interacts with a portion of the BTK kinase domain defined by the coordinates.

18. (Previously Presented) The method according to claim 17 further comprising:
assaying the identified compound for modulation of BTK kinase activity.
19. (Cancelled)
20. (Currently Amended) A method for preparing a ~~the crystal of the BTK kinase domain of~~ claim 1 comprising:
preparing a purified BTK kinase domain; and
crystallizing the BTK kinase domain at 4 °C using a hanging drop method, wherein the drop comprises 2 microliters of from a solution comprising 2mg/ml of the purified BTK kinase domain and 1 microliter of reservoir solution and is equilibrated with 600 microliters of the reservoir solution, wherein the reservoir solution comprises 20% polyethylene glycol, 100 mM Tris/HCl, and 1 mM DTT, the reservoir solution being buffered at a pH of about 8.0.
21. (Currently Amended) A crystal ~~of the BTK kinase domain of claim 1~~ prepared by the ~~process~~ process of claim 20.
22. (New) The method of claim 16, wherein the crystal is obtained by a method comprising:
preparing a purified BTK kinase domain; and
crystallizing the BTK kinase domain at 4 °C using a hanging drop method, wherein the drop comprises 2 microliters of a solution comprising 2mg/ml of purified BTK kinase domain and 1 microliter of reservoir solution and is equilibrated with 600 microliters of the reservoir solution, wherein the reservoir solution comprises 20% polyethylene glycol, 100 mM Tris/HCl, and 1 mM DTT, the reservoir solution being buffered at a pH of about 8.0.
23. (New) The method of claim 17, wherein the crystal is obtained by a method comprising:

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preparing a purified BTK kinase domain; and
crystallizing the BTK kinase domain at 4 °C using a hanging drop method, wherein the drop comprises 2 microliters of a solution comprising 2mg/ml of purified BTK kinase domain and 1 microliter of reservoir solution and is equilibrated with 600 microliters of the reservoir solution, wherein the reservoir solution comprises 20% polyethylene glycol, 100 mM Tris/HCl, and 1 mM DTT, the reservoir solution being buffered at a pH of about 8.0.

(New) A method of identifying a ligand than binds a BTK kinase domain, comprising:
preparing one or more crystal of the BTK kinase domain by the method of claim 20;
incubating said one or more crystal in the presence of a candidate ligand; and
identifying a ligand that binds to said one or more crystal.